Short-term exposure to ambient fine particulate matter and out-of-hospital cardiac arrest: a nationwide case-crossover study in Japan

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Summary

Background $PM_{2.5}$ is an important but modifiable environmental risk factor, not only for pulmonary diseases and cancers, but for cardiovascular health. However, the evidence regarding the association between air pollution and acute cardiac events, such as out-of-hospital cardiac arrest (OHCA), is inconsistent, especially at concentrations lower than the WHO daily guideline (25 μg/m³). This study aimed to determine the associations between exposure to ambient air pollution and the incidence of OHCA.

Methods In this nationwide case-crossover study, we linked prospectively collected population-based registry data for OHCA in Japan from Jan 1, 2014, to Dec 31, 2015, with daily $PM_{2.5}$, carbon monoxide (CO), nitrogen dioxide (NO_2), photochemical oxidants (O_x), and sulphur dioxide (SO_2) exposure on the day of the arrest (lag 0) or 1–3 days before the arrest (lags 1–3), as well as the moving average across days 0–1 and days 0–3. Daily exposure was calculated by averaging the measurements from all $PM_{2.5}$ monitoring stations in the same prefecture. The effect of $PM_{2.5}$ on risk of all-cause or cardiac OHCA was estimated using a time-stratified case-crossover design coupled with conditional logistic regression analysis, adjusted for daily temperature and relative humidity. Single-pollutant models were also investigated for the individual gaseous pollutants (CO, NO_2, O_x, and SO_2), as well as two-pollutant models for $PM_{2.5}$ with these gaseous pollutants. Subgroup analyses were done by sex and age.

Findings Over the 2 years, 249 372 OHCAs were identified, with 149 838 (60·1%) presumed of cardiac origin. The median daily $PM_{2.5}$ was 11·98 μg/m³ (IQR 8·13–17·44). Each 10 μg/m³ increase in $PM_{2.5}$ was associated with increased risk of all-cause OHCA on the same day (odds ratio [OR] 1·016, 95% CI 1·009–1·023) and at lags of up to 3 days, ranging from OR 1·015 (1·008–1·022) at lag 1 to 1·033 (1·023–1·043) at lag 0–3. Results for cardiac OHCA were similar (ORs ranging from 1·016 [1·007–1·025] at lags 1 and 2 to 1·034 [1·021–1·047] at lag 0–3). Patients older than 65 years were more susceptible to $PM_{2.5}$ exposure than younger age groups but no sex differences were identified. CO, O_x, and SO_2 were also positively associated with OHCA while NO_2 was not. However, in two-pollutant models of $PM_{2.5}$ and gaseous pollutants, only $PM_{2.5}$ (positive association) and NO_2 (negative association) were independently associated with increased risk of OHCA.

Interpretation Short-term exposure to $PM_{2.5}$ was associated with an increased risk of OHCA even at relatively low concentrations. Regulatory standards and targets need to incorporate the potential health gains from continual air quality improvement even in locations already meeting WHO standards.

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Introduction

The adverse health effects of air pollution have been established in epidemiological studies over recent decades. At a global scale, ambient air pollution was responsible for 4·1 million deaths in 2016.[1] As the most extensively studied type of air pollution, $PM_{2.5}$ is accepted to have causal associations with cardiovascular disease.[2,3] Several independent groups have observed cardiovascular outcomes associated with $PM_{2.5}$ exposures lower than existing standards and guidelines such as the WHO daily 24-h average guideline value of 25 μg/m³.[4,5]

Out-of-hospital cardiac arrest (OHCA) is a major medical emergency and public health problem, with global survival rates of less than 10%.[6] Growing evidence supports the associations between acute air pollution exposure and OHCA risk in case-crossover studies.[7–9] However, inconsistent results for $PM_{2.5}$ and gaseous pollutants have also been reported, especially with $PM_{2.5}$ levels lower than the WHO standard.[9–11] A study[12] of 5973 cases in Stockholm, for example, found no association between $PM_{2.5}$ and OHCA where the average daily $PM_{2.5}$ was 8·1 μg/m³, although others have found positive associations with similar $PM_{2.5}$ exposure.[7,13] These results indicate that a larger-scale study will be helpful to elucidate associations in areas with low $PM_{2.5}$ concentrations. In addition, the acute risks from air pollution have been well characterised for susceptible people such as those older than 75 years of age,[3] but less

Research in context

Evidence before this study

Out-of-hospital cardiac arrest (OHCA) is a major medical emergency and public health problem, with global survival rates at less than 10%. Given the dismal prognosis, preventive strategies are the best solution. In addition to the modification of individual risk factors, growing evidence supports concern about ambient air pollution and its association with cardiovascular diseases including OHCA. However, results regarding the short-term exposure to ambient $PM_{2·5}$ and the incidence of OHCA have been inconsistent in previous studies, especially at $PM_{2·5}$ levels lower than the WHO standard (25 μg/m^3). Moreover, vulnerable groups such as older people who are exposed to air pollution consistently exhibit enhanced risk in epidemiological studies; however, less is known about sex differences. All main previous reports on the topic known to us are listed in the appendix (p 10).

Added value of this study

This nationwide case-crossover study in Japan shows an independent association between increase in daily $PM_{2·5}$ exposure and risk of OHCA, even at $PM_{2·5}$ levels lower than regulation standard and guidelines. The study includes 249 372 all-cause OHCAs, of which 149 838 were due to cardiac causes. No sex dimorphisms were observed. To our knowledge, this is by far the largest case-crossover study on this topic to estimate the risk and detect susceptible populations. Our data also show the association between short-term exposure to carbon monoxide, photochemical oxidants, and sulphur dioxide and increased risk of all-cause OHCAs, but not with nitrogen dioxide.

Implications of all the available evidence

Despite the air quality of the study generally meeting the current standards, significant associations between $PM_{2·5}$ and OHCA were observed. These facts, combined with previous publications, suggest the requirement for world leaders, governments, and policy makers to reassess the current air quality standards and to improve air quality further. As no boundary exists in air quality between countries, a global approach to tackle this crucial health issue is necessary for our planet.

is understood about sex differences. A larger study could assist in characterising associations and detecting specific population subgroups for better protection.

Thus, we did this nationwide case-crossover study in Japan with OHCA cases from the All-Japan Utstein registry to determine the associations between short-term exposure to ambient air pollution and the incidence of OHCA.

Methods

Study area and outcome data

Japan has a territory of 377 973·89 km² with 47 prefectures, and had a population of 127·1 million in 2015.[14] The OHCA records we used were collected by the All-Japan Utstein registry of the Fire and Disaster Management Agency (FDMA) of Japan, from Jan 1, 2014, to Dec 31, 2015. The FDMA is responsible for emergency medical responses, and there were 752 fire stations with an ambulance dispatch centre in 2014.[15]

Details of the registry have been described previously.[16] Briefly, it consists of a nationwide, prospectively collected repository of OHCA data, which is recorded according to the Utstein-style internationally standardised reporting guidelines.[17] Each record includes patient information about the location, date, sex, age, OHCA origin, and other core data elements, recorded by the local emergency medical service personnel managed by the FDMA.

Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[17] Cardiac arrests were classified as being of cardiac or non-cardiac origin. Non-cardiac origins were further classified into cerebrovascular disease, respiratory disease, malignant tumour, trauma, submersion, drug overdose, or any other non-cardiac causes. These origins were determined by the physicians in charge at the emergency medical service. This study was approved by the Tasmanian Human Research Ethics Committee (H0017657).

Ambient air pollution and meteorological data

Data on $PM_{2·5}$ and gaseous pollutants including carbon monoxide (CO), nitrogen dioxide (NO_2), photochemical oxidants (O_x), and sulphur dioxide (SO_2) were obtained from the Environmental Database of the National Institute for Environmental Studies, Japan.[18] Each prefecture in Japan has several city-based $PM_{2·5}$ monitoring stations. The daily $PM_{2·5}$ for each prefecture was calculated by averaging the measurements from all stations in the prefecture. The differences between daily maximum and minimum $PM_{2·5}$ concentrations from these stations within the same day and the same prefecture were also calculated. The means of these maximum differences within 1 year were then calculated from each prefecture for subsequent sensitivity analysis. Daily averages for each prefecture for gaseous pollutants were calculated from hourly concentrations of CO, NO_2, O_x, and SO_2.

Meteorological data were from Japan's weather stations, the Local Meteorological Observatories, and included daily temperature and relative humidity. These were obtained for the study period from the Japan Meteorologic Agency website.[19] We calculated daily meteorological data for each prefecture by averaging daily mean temperature and relative humidity from all Local Meteorological Observatory stations each day, excluding those in non-habitable areas with extreme conditions (eg, on top of Mount Fuji). A correlation matrix was constructed between

ambient air pollution and meteorological variables to avoid any potential collinearity issue.

Statistical analysis

The linked data were analysed using a time-stratified case-crossover design coupled with conditional logistic regression analysis. The time-stratified case-crossover design was first proposed in 1991 by Maclure[20] and is a well established study design to assess the association between transient exposure to air pollution and emergency health events; it is a common design in air pollution epidemiological studies.[8,9] The day the OHCA occurred is defined as the case day, whereas the days of the same day of the week during the same month and year (eg, all other Tuesdays of the same month and year) were controls. Each individual patient thus acts as their own control as the study design compares the exposure on the case day with exposure on the control days. This design has been verified as an efficient approach to control time-independent and time-dependent confounders in evaluating short-term health impacts associated with air pollution.[21]

The main analysis was the multivariable model of the effects of $PM_{2·5}$. Odds ratios (ORs) and their 95% CIs were estimated using a conditional logistic regression model by merging the air quality and meteorological data at the prefecture level with each OHCA case. Since the response period of the incidence of OHCA after exposure to air pollution is unknown, the analyses were done with lagged exposures for 0–3 days, on the basis of previous case-crossover studies.[7–9,13] Lag 0 was the average exposure concentration on the day of the OHCA, lag 1 was the average exposure concentration on the day before the OHCA, and so forth. The moving average of 0–1 day (lag 0–1) was calculated by averaging the exposure of the day of the OHCA episode and the day preceding the OHCA. The average exposure of 3 days before the OHCA and the day of the OHCA was defined as lag 0–3. Meteorological data including temperature and relative humidity during the same lag period were used as potential confounders in the multivariable model. We modelled temperature and relative humidity as a natural cubic spline with three degrees of freedom to test the possible non-linear effects of meteorological variables. We chose other degrees of freedom as sensitivity analyses. Single-pollutant models for the effects of CO, NO_2, O_x, and SO_2 on OHCAs were run separately to the main analysis, and two-pollutant models were also investigated for $PM_{2·5}$ with other gaseous pollutants (CO, NO_2, O_x, and SO_2).

To better understand the association between ambient air exposure and different origins of OHCAs, separate analyses were done for all-cause OHCAs and the arrests presumed to have cardiac causes in both the single-pollutant and two-pollutant models. Additional stratification for sex and age (≤35 years, 36–64 years, 65–74 years, and ≥75 years) were also investigated for $PM_{2·5}$.

	2014 (n=125 951)	2015 (n=123 421)	Total (n=249 372)
Age, years	74·3 (17·4)	74·6 (17·3)	74·4 (17·4)
≤35	4991 (4·0%)	4744 (3·8%)	9735 (3·9%)
36–64	21 865 (17·4%)	20 704 (16·8%)	42 569 (17·1%)
65–74	22 622 (18·0%)	22 302 (18·1%)	44 924 (18·0%)
≥75	76 473 (60·7%)	75 671 (61·3%)	152 144 (61·0%)
Sex			
Female	54 206 (43·0%)	53 000 (42·9%)	107 206 (43·0%)
Male	71 745 (57·0%)	70 421 (57·1%)	142 166 (57·0%)
OHCA origin			
Cardiac	76 141 (60·5%)	73 697 (59·7%)	149 838 (60·1%)
Non-cardiac	49 810 (39·5%)	49 724 (40·3%)	99 534 (39·9%)
Cerebrovascular diseases	4085 (3·2%)	3945 (3·2%)	8030 (3·2%)
Respiratory diseases	10 296 (8·2%)	10 561 (8·6%)	20 857 (8·4%)
Malignant tumours	3779 (3·0%)	3904 (3·2%)	7683 (3·1%)
External causes	8592 (6·8%)	7803 (6·3%)	16 395 (6·6%)
Other non-cardiac causes	23 058 (18·3%)	23 511 (19·0%)	46 569 (18·7%)

Data are mean (SD) or n (%). Each year contributed approximately 50% to the total for each category. OCHA=out-of-hospital cardiac arrest.

Table 1: **Characteristics of the study participants with OHCAs, by year**

Furthermore, we did sensitivity analyses for the prefectures that had an annual mean maximum difference in $PM_{2·5}$ concentrations of less than 10 μg/m³, as well as four specific prefectures reflecting various sources of pollutants (Tokyo and Osaka as major cities with pollutants from vehicles, and Hyogo and Nagasaki as coastal cities with pollutants from ships). ORs were expressed as per unit change in CO and per 10-unit change in $PM_{2·5}$, NO_2, O_x, and SO_2. A correlation analysis was done to describe the relationship between ambient air pollutants and meteorological variables, expressed with the Pearson correlation coefficient *r*. All analyses were done using R version 3.5.0.

Role of the funding source

There was no funding source for this study. BZ and KN had access to all the data. All authors were responsible for the decision to submit the manuscript.

Results

249 372 OHCAs were documented during the 2 years of study (table 1). The mean age of patients affected was 74·4 years (SD 17·4) and 57% were male. 149 838 (60·1%) of the included OHCAs were presumed to have cardiac origin. Of 99 534 patients with OHCAs of non-cardiac origin, 20 857 arrests were caused by respiratory diseases and 8030 were caused by cerebrovascular diseases (table 1). 245 614 (98·5%) of the OHCAs occurred while $PM_{2·5}$ concentrations were lower than the Japan or USA standards of 35 μg/m³, and 229 233 (91·9%) occurred at concentrations lower than the WHO standard of 25 μg/m³ (figure 1).

Summary statistics of daily ambient air quality and meteorological data show median $PM_{2·5}$ levels of

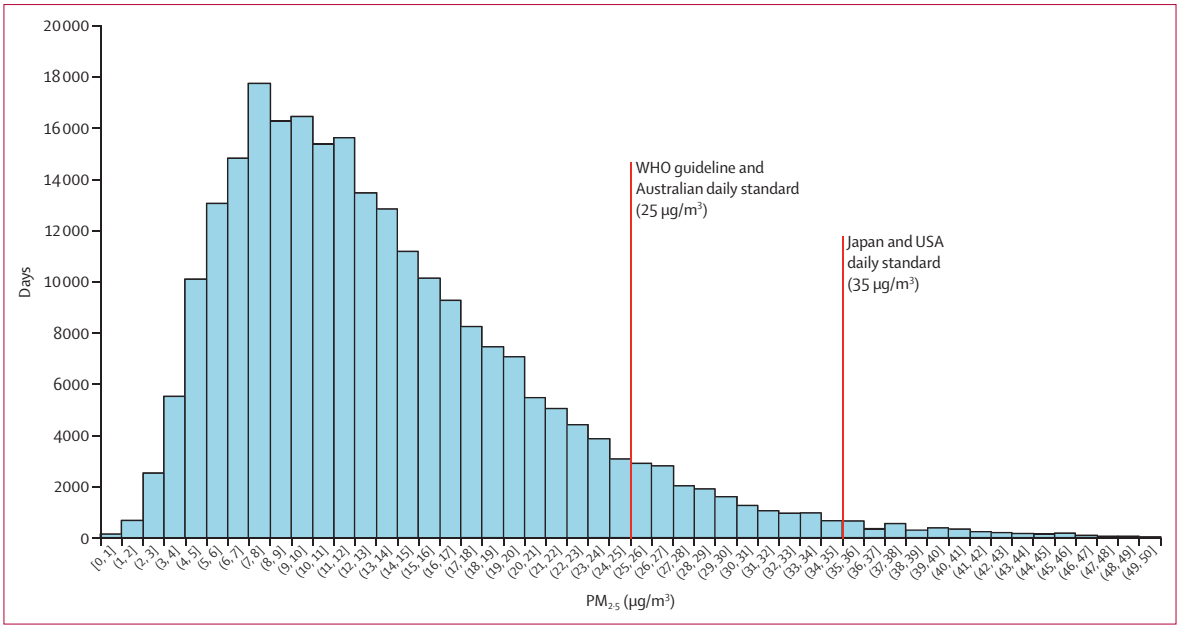

Figure 1: **Distribution of daily $PM_{2·5}$ levels on OHCA event days**
$PM_{2·5}$ categories are denoted with interval notation: parentheses indicate excluded endpoints whereas square brackets indicate included endpoints. OHCA=out-of-hospital cardiac arrest.

	Days missing data	Mean (range)	Percentile					IQR
			5%	25%	50%	75%	95%	
$PM_{2·5}$ (μg/m³)	11	13·62 (0·27 to 71·01)	4·61	8·13	11·98	17·44	28·37	9·31
CO (ppm)	35	0·35 (0·0 to 1·41)	0·18	0·27	0·33	0·41	0·57	0·14
NO_2 (ppb)	2	9·75 (0·0 to 45·02)	3·45	5·91	8·55	12·37	20·19	6·46
O_x (ppb)	2	30·51 (2·22 to 79·20)	13·50	22·96	29·93	37·31	49·53	14·35
SO_2 (ppb)	2	1·83 (0·0 to 106·75)	0·38	0·93	1·52	2·37	4·28	1·44
Temperature (°C)	0	15·2 (−10·2 to 32·1)	1·7	8·0	16·2	22·0	27·5	14·0
Humidity	0	72% (0 to 100)	50%	64%	73%	81%	91%	17%

34 310 datapoints were included for each parameter. CO=carbon monoxide. NO_2=nitrogen dioxide. O_x=photochemical oxidants. SO_2=sulphur dioxide. ppm=parts per million. ppb=parts per billion. OHCA=out-of-hospital cardiac arrest.

Table 2: **Description of daily ambient air pollutants and meteorological data for the days of OHCAs**

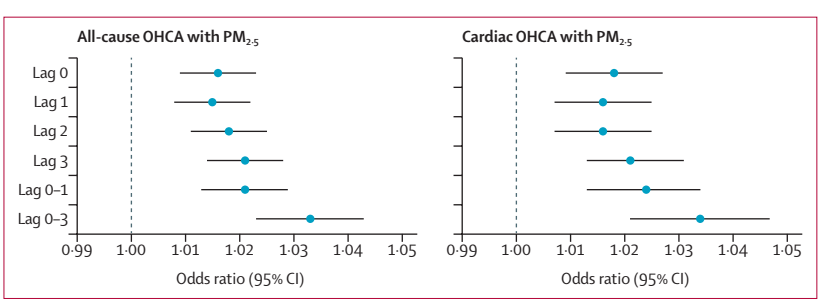

Figure 2: **Association of OHCA with daily lag exposure to $PM_{2·5}$**
Odds ratios are per 10-unit change in $PM_{2·5}$ exposure. Models were adjusted for temperature and humidity. Lags 0–1 and 0–3 represent moving averages. OHCA=out-of-hospital cardiac arrest.

See Online for appendix

11·98 μg/m³ (IQR 8·13–17·44) and NO_2 levels of 8·55 parts per billion (ppb; IQR 5·91–12·37; figure 1; table 2). The number of monitoring stations and mean of maximum differences of $PM_{2·5}$ concentrations for each prefecture are shown in the appendix (p 2), alongside a scatterplot matrix of the air pollutants and meteorological data (appendix p 25). $PM_{2·5}$ concentrations were moderately or weakly positively correlated with other air pollutants (r<0·43). O_x was moderately negatively correlated with CO, whereas NO_2 showed a weak positive correlation with SO_2 (appendix p 25). Temperature and humidity were weakly correlated with air pollutants; humidity was negatively correlated whereas the direction of correlation oscillated for temperature. Therefore, these variables were put into the same model.

When examining the association between daily lag exposure to $PM_{2·5}$ and OHCA, positive associations were observed for all lags, with an increased risk of all-cause OHCA ranging from OR 1·015 (95% CI 1·008–1·022)

at lag 1 to 1·033 (1·023–1·043) at lag 0–3 per 10 μg/m³ increase in $PM_{2·5}$ exposure, and an OR of 1·016 (1·009–1·023) on the same day (ie, lag 0; figure 2; appendix p 5). Similarly, significant associations were shown between cardiac OHCA and $PM_{2·5}$ exposures at all lags, with an increased risk ranging from 1·016 (1·007–1·025) at lags 1 and 2 to 1·034 (1·021–1·047) at lag 0–3 per 10 μg/m³ increase in $PM_{2·5}$. Effect size estimates were generally greater for average exposure over lag 0–3 than for individual lags or lag 0–1.

These findings were corroborated in sensitivity analyses for prefectures with an annual mean maximum difference in $PM_{2·5}$ concentrations of less than 10 μg/m³. The excess risk of OHCA associated with $PM_{2·5}$ exposure at all lags remained similar to those for the whole population for all-cause OHCA (ranging from OR 1·017 [95% CI 1·005–1·030] at lag 1 to 1·038 [1·021–1·056] at lag 0–3) and cardiac OHCA (ranging from 1·019 [1·003–1·035] at lag 0 to 1·039 [1·017–1·062] at lag 0–3; appendix p 3). Similar effects sizes but fewer significant associations (due to smaller sample sizes and statistical power) between $PM_{2·5}$ and OHCA were observed in Tokyo, Osaka, and Hyogo (appendix p 3). Significant and robust estimates (OR 1·040–1·065) were seen for lag 0–3 in each representative prefecture, except for Nagasaki, which had fewer OHCAs (n=2560) than the other representative prefectures (ranging from 9625 cases in Hyogo to 25 387 in Tokyo; appendix p 3).

In the stratified analysis, both sexes had similar effect estimates for the association between short-term $PM_{2·5}$ exposure and all-cause OHCA, with increased risk ranging from OR 1·015 (1·006–1·024) at lag 1 to 1·032 (1·019–1·045) at lag 0–3 for men and from 1·014 (1·004–1·025) at lag 1 to 1·035 (1·020–1·050) at lag 0–3 for women, although the association was not significant for women at lag 0 (figure 3; appendix p 5). Among patients older than 65 years, $PM_{2·5}$ exposures over all 4 days considered were significantly associated with incidence of all-cause OHCA (figure 3). The estimates of increased risk were similar between those aged 65–74 years and those aged 75 years or older (figure 3). No significant associations were detected for patients younger than 64 years, except for the patients aged 36–64 years at lag 3 (appendix p 5).

Similar findings were observed for cardiac OHCAs (figure 3). No sex-attributable dimorphism was seen in the excess risks for OHCA with cardiac origin (ranging from OR 1·016 [95% CI 1·005–1·028] at lag 2 to 1·035 [1·018–1·052] at lag 0–3 in men and from 1·015 [1·002–1·029] at lags 1 and 2 to 1·033 [1·014–1·053] at lag 0–3 in women, again with no significant association for women at lag 0; appendix p 6). Similar to all-cause OHCA, no associations between short-term $PM_{2·5}$ exposure and cardiac OHCA were identified for patients younger than 65 years. Significant associations were found in patients aged 75 years or older across all 4 days. In those aged 65–74 years, however, excess risks of cardiac OHCA were only significant at lags 0, 0–1, and 0–3, although the effect sizes were similar to those of all-cause OHCA (figure 3; appendix p 6).

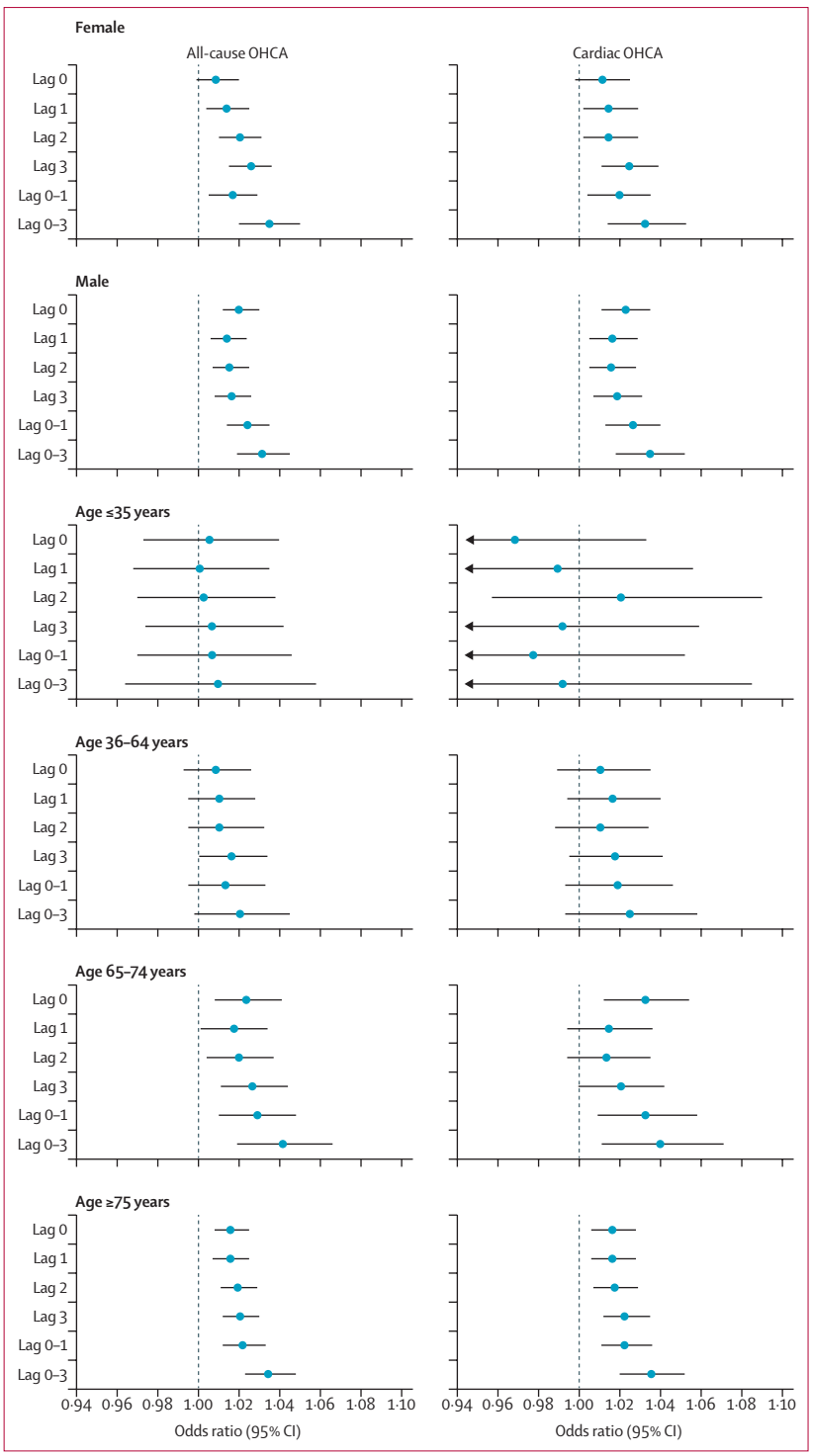

Figure 3: **Association of all-cause and cardiac-cause OHCA with daily lag exposure to $PM_{2·5}$ by sex and age**
Odds ratios are per 10-unit change in $PM_{2·5}$ exposure. Models were adjusted for temperature and humidity. OHCA=out-of-hospital cardiac arrest.

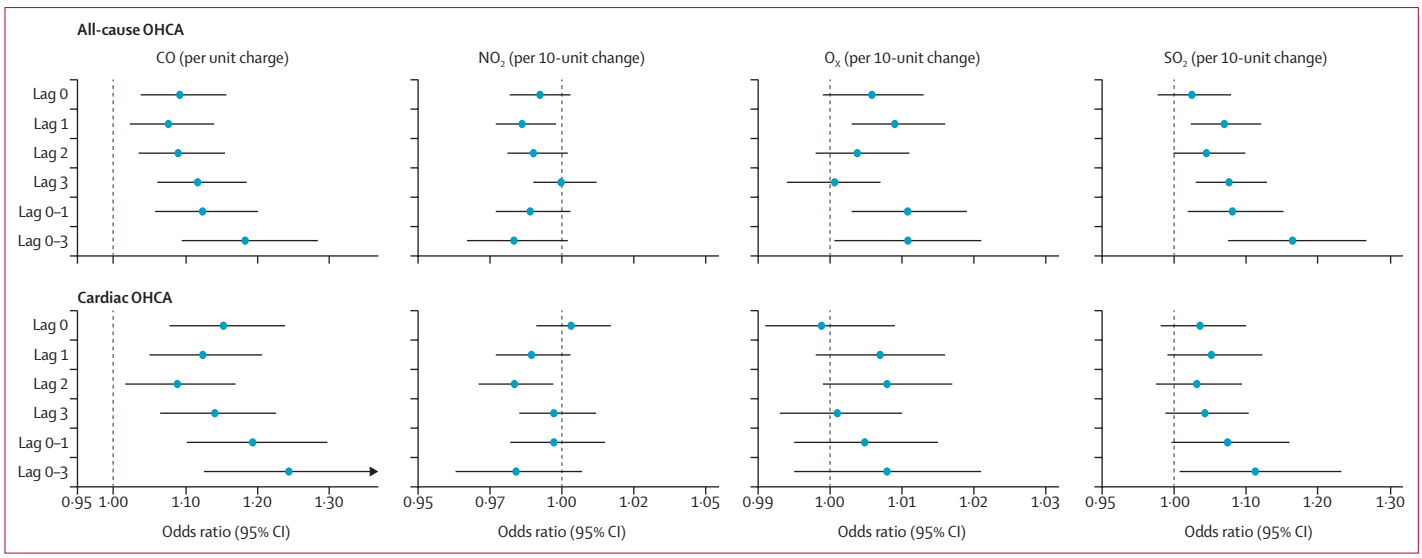

Figure 4: **Association of OHCA with daily lag exposure to gaseous pollutants**
Model was adjusted for temperature and humidity. OHCA=out-of-hospital cardiac arrest. CO=carbon monoxide. NO_2=nitrogen dioxide. O_x=photochemical oxidants. SO_2=sulphur dioxide.

In the stratification by age and sex, we also did sensitivity analyses for all-cause OHCA and cardiac OHCA in prefectures with annual mean maximum differences in $PM_{2·5}$ concentrations of less than 10 μg/m³ (appendix p 4). The results followed a similar pattern to the main analyses, with slightly higher risk estimates but fewer significant associations. For all-cause OHCA, increased risks were found in men (ranging from OR 1·019 [95% CI 1·003–1·036] at lag 1 to 1·040 [1·017–1·063] at lag 0–3) and patients aged 75 years or older (from 1·022 [1·007–1·038] at lag 1 to 1·051 [1·029–1·073] at lag 0–3) over all 4 days; increased risks were also found for women at lags 2, 3, and 0–3, ranging from 1·022 (1·004–1·041) at lag 2 to 1·036 (1·011–1·062) at lag 0–3 (appendix p 4). For cardiac OHCA, similar associations were observed with $PM_{2·5}$ between sexes, although fewer were significant (appendix p 4). Significant associations ranged from 1·023 (1·002–1·045) at lag 2 to 1·040 (1·011–1·071) at lag 0–3 for men and occurred only at lag 3 (1·026 [1·002–1·051]) and lag 0–3 (1·037 [1·004–1·072]) for women (appendix p 4). Increased risks were still found across all 4 days for patients older than 75 years, ranging from 1·025 (1·006–1·045) at lag 1 to 1·055 (1·028–1·083) at lag 0–3 (appendix p 4).

In the single-pollutant models of other pollutants, significantly positive effects were observed for CO, O_x, and SO_2 on all-cause OHCA. Each 1 parts-per-million increase in CO was associated with the increased risks of OHCA, ranging from OR 1·080 (95% CI 1·023–1·140) at lag 1 to 1·185 (1·095–1·284) at lag 0–3 (figure 4). Each 10 ppb increase in O_x was associated with increased OHCA risk at lags 1, 0–1, and 0–3, from 1·009 (1·003–1·016) at lag 1 to 1·011 (1·001–1·021) at lag 0–3. For SO_2, these increased risks were present at lags 1, 3, 0–1, and 0–3, ranging from 1·071 (1·023–1·121) at lag 1 to 1·167 (1·075–1·267) at lag 0–3 per 10 ppb increase (figure 4). Interestingly, NO_2 exposure was negatively associated with all-cause OHCA at lag 1 (figure 4; appendix p 7).

Among patients with OHCA of cardiac origin, the risk estimates for CO mostly became stronger, except for at lag 2, which was similar to all-cause OHCAs (figure 4). For SO_2, the only increased risk was 1·122 (1·008–1·247) at lag 0–3. No significant associations were found for O_x with cardiac OHCA (figure 4; appendix p 7). NO_2 had negative association at lag 2 (figure 4; appendix p 7).

In two-pollutant models for all-cause and cardiac OHCAs, the association of $PM_{2·5}$ remained significant over all 4 days, except for at lags 0 and 1 for cardiac OHCAs in the $PM_{2·5}$ plus CO model, and the associations of CO, O_x, and SO_2 disappeared (appendix pp 8–9, 26). Greater risk estimates were observed for $PM_{2·5}$ when models included NO_2 compared with the single pollutant models, whereas the association of NO_2 remained negative (appendix pp 8–9, 26).

Sensitivity analyses achieved by varying the degrees of freedom for the temperature and relative humidity in the above models confirmed our results (appendix pp 13–24). No differences in statistical significance were observed among different degrees of freedom.

Discussion

In this large case-crossover study of OHCA, we showed that daily increases in $PM_{2·5}$ exposure up to 3 days before were associated with increased risks in both all-cause and cardiac OHCA, even at concentrations lower than existing air quality standards. We also found older people were more susceptible to the exposure (all-cause OHCA in patients aged ≥65 years and cardiac OHCA in patients

aged ≥75 years) without apparent sex differences. Exposure to other pollutants, such as CO, O_x, and SO_2, as associated with higher risk of all-cause OHCA in single-pollutant models, except for NO_2. When investigated in two-pollutant models, the association of $PM_{2·5}$ remained unchanged whereas the significant association of other gaseous pollutants diminished. These results support the need for re-evaluation of air quality standards to reduce associated adverse health outcomes.

This study has several strengths. First, to our knowledge, this was the largest study on short-term exposure to ambient air pollutants and OHCA, including 249 372 cases—approximately three times as many as the total number of OHCAs reported in preceding articles (appendix p 10), where the largest single study included 21 509 OHCAs.[22] This sample size provided sufficient statistical power to estimate the risk not only in the whole population but in subgroup analyses by age and sex. The use of the All-Japan Utstein Registry, the Japanese nationwide registry of OHCAs, allowed us to capture the information of every case treated by emergency medical service personnel in Japan with minimal selection bias. The use of Utstein-style registry assured the quality of OHCA data. Furthermore, the case-crossover study design helped to avoid potential confounding factors as individual characteristics and other variables do not vary during the case and control periods.

In this study, short-term exposure to $PM_{2·5}$ was significantly associated with increased risk of OHCA. These findings corroborate other case-crossover studies of OHCAs.[7–9,23–25] A study including 11 677 OHCA cases in Houston found that each 6 μg/m³ increase in $PM_{2·5}$ up to 2 days before was associated with OHCA occurrence, and the strongest association was an increase of 4·6% at lag 1–2 days.[9] Similar results have also been reported in New York City,[8] Melbourne,[7] Perth,[23] Copenhagen,[24] and Indianapolis.[25] Our results also support the findings from US Medicare data, which showed significant association between short-term exposures to $PM_{2·5}$ and mortality.[5] In the review of global cardiovascular morbidity and mortality attributed to air pollution, the relative risk of acute cardiovascular events increases 1–3% for short-term exposure to $PM_{2·5}$ within a few days,[26] which corresponds to the increased risks found in this national study. Combined with air quality forecasts, our results can be used to predict this emergency condition and to allocate resources more efficiently.

WHO and various countries have set air quality guidelines or standards to protect human health (appendix p 11). More than 90% of OHCAs in our study occurred with $PM_{2·5}$ levels lower than the WHO guideline and Australian standard daily average concentration of 25 μg/m³, while 98·5% of them happened at levels lower than the Japanese or American daily standard level of 35 μg/m³. Our observations corroborate with findings in previous reports[7,25] where $PM_{2·5}$ levels were less than 10 μg/m³ (6·4 and 8·7 μg/m³; appendix p 10), although in a separate study, no association was shown between $PM_{2·5}$ and OHCA with an average $PM_{2·5}$ level of 8·1 μg/m³.[12] To date, no threshold level of $PM_{2·5}$ is advised as safe for the general population.[5,26] Given the growing body of evidence in areas with poor air quality or even where the target standard has been achieved, current air quality standards need to be reassessed with consideration for efficient strategies to reduce air pollutants to as low a level as possible.

Older people have been found to be more susceptible than younger age groups in previous studies.[7,9] Our findings from age-stratified analyses were similar to previous case-crossover studies in OHCA in Melbourne[7] and Indianapolis,[25] and also in line with a report on mortality among the US Medicare population.[5] The acute impact of $PM_{2·5}$ has been found to present primarily on older people or other susceptible groups.[3] Additionally, some previous studies[7,9] have indicated men had higher risk, although no sex differences have been shown in others.[8,24,25] Our study also found no sex differences, especially after adjusting for temperature and humidity.

Results have varied in previous studies of gaseous pollutants and OHCA. Despite some null results in the literature,[10] significant positive associations between CO and OHCA have been documented[7,23,24,27] and associations with SO_2 have also been observed.[27–29] Growing evidence of links between ozone (O_3) and OHCA have been observed in several case-crossover or time-series studies.[9,12,13,28–30] A study in Stockholm only found short-term effects of O_3 on OHCA but not for other air pollutants including $PM_{2·5}$.[12] Reasons could include the differences in concentration and composition of air pollutants, study design, and characteristics of study participants. A study in Seoul[27] with a large sample size of 21 509 OHCA cases found an independent association with $PM_{2·5}$ but with the effects of the gaseous pollutants generally diminished in two-pollutant models of $PM_{2·5}$ with gaseous pollutants; these results are similar to our findings, with both studies set in Asian countries.

Negative associations between NO_2 and OHCA were observed in both single-pollutant and two-pollutant models, with a daily average concentration of NO_2 of 9·75 ppb. Heterogeneous associations have been reported in previous studies on short-term exposure to NO_2 and association with OHCA (appendix p 12). The discrepancies among the reports can be explained by the varying NO_2 levels of the areas studied. In low NO_2 concentration areas, null or negative associations have been reported. Two previous case-crossover studies[12,13] showed significantly negative associations, with average NO_2 levels of 12·8 ppb and 8·3 ppb, similar to ours. Five studies have shown null results, in which average NO_2 levels were less than 13 ppb in three studies and the other two showed median NO_2 of 3 ppb and 27 ppb.[7–9,23,24] However, increased risks from acute NO_2 exposure on OHCA were observed in Chinese cities[22,29] and in South Korea,[27] where the average NO_2 levels were greater

than 17 ppb. The discrepancies across these studies indicate the possibility of a threshold concentration with short-term exposure to NO_2 and OHCA onset.

This study should be interpreted in the context of several limitations. We assigned the daily average of air pollutant level in each prefecture to individuals owing to the absence of finer-scaled OHCA data. This is a common approach in air pollution epidemiology, and it is acknowledged that this will introduce exposure misclassification. The assumption of homogeneous exposure across the prefecture could lead to non-differential measurement error that will probably bias our results towards the null and underestimate the true relationship. However, the sensitivity analyses for prefectures with very low spatial variation in air quality as defined as the mean of maximum differences of $PM_{2·5}$ concentrations less than 10 μg/m³ showed consistent results with the main analysis, confirming the robust nature of the findings. The prefecture-level analysis had similar results to the nationwide analyses, but less statistical power to detect the associations between $PM_{2·5}$ and OHCA (type II error). Thus, our nationwide data did not mask the association, instead revealing the association by using the power of a large dataset. Japan is a long, island country and has extremely high population density in urban areas that contain most of the air quality monitoring sites, with most air quality stations being representative of population exposures. Future studies are warranted on the effects of the emission sources and constituents of $PM_{2·5}$ because they could play an incremental role in these associations. Nonetheless, our methodology and findings were consistent with previous reports that only focused on the size of the air pollution (ie, $PM_{2·5}$) and consolidate discrepancies among the findings from previous publications. Another limitation is absence of information about the personal risk factors of cardiovascular disease for our participants. Although these factors have minimal influence on the analysis because each patient serves as their own control in this study design, the evaluation of further potential individual risk factors is impossible without records of these details.

In conclusion, this national case-crossover study including OHCA cases from 2014 to 2015 found that short-term exposure to ambient air pollutants was associated with increased risk of OHCA onset, and $PM_{2·5}$ was associated with OHCA, independently of the effects of CO, NO_2, O_x and SO_2. The finding of adverse effects when air pollutant levels are below established air quality standards raises the urgent need to reassess current standards and improve air quality.

Contributors

All authors were involved in the design and planning of the study. MK and KN collected the data. BZ, FHJ, FS, and KN were involved in all statistical elements of study design and analysis of the results. BZ drafted the first manuscript. FHJ, FS, MK, and KN critically revised the manuscript. All authors contributed to the interpretation of the results and approved the final version for publication. KN is guarantor for the study.

Declaration of interests

We declare no competing interests.

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